

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/10, 9/08		A2	(11) International Publication Number: WO 99/32152 (43) International Publication Date: 1 July 1999 (01.07.99)
(21) International Application Number: PCT/US98/27410		(74) Agents: BURKE, John, E. et al.; Pillsbury Madison & Sutro, LLP, 1100 New York Avenue, N.W., Washington, DC 20005 (US).	
(22) International Filing Date: 23 December 1998 (23.12.98)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: PCT/US97/23865 23 December 1997 (23.12.97) US		(71) Applicant (<i>for all designated States except US</i>): MDV TECHNOLOGIES, INC. [US/US]; 3040 Science Park Road, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): KHARITONOV, Vladimir [RU/US]; 2536 San Clemente Terrace, San Diego, CA 92122 (US). RANNEY, Helen, M. [US/US]; 6229 La Jolla Mesa Drive, La Jolla, CA 92037 (US). TREVINO, Leo [US/US]; Apartment 5210, 7665 Palmilla Drive, San Diego, CA 92122 (US). FLORE, Stephen, G. [US/US]; 3899 Nobel Drive #1308, San Diego, CA 92122 (US). DELLAMARY, Luis, A. [MX/US]; 838 Redberry Court, San Marcos, CA 92069 (US). REEVE, Lorraine, E. [US/US]; 6192 Webster Church Road, Dexter, MI 48130 (US). WEERS, Jeffry, G. [US/US]; 12191 Salix Way, San Diego, CA 92129 (US).	
(54) Title: METHODS FOR DELIVERING PHARMACEUTICAL AGENTS TO MUCOSAL SURFACES			Published <i>Without international search report and to be republished upon receipt of that report.</i>
(57) Abstract			
Delivery systems and methods of delivering pharmaceutical agents to a hydrophobic region of an animal, particularly a mucosal surface, such as the mucosal lining of the gastrointestinal (GI) tract, are disclosed. In one embodiment, one or more pharmaceutical agents are incorporated into a delivery system comprising a constitutive polymer, such as a poloxamer, and, optionally, one or more modifier polymers (e.g., carboxymethylcellulose) and/or one or more hydrophilic co-surfactants (e.g., a fatty acid soap). In another embodiment, one or more pharmaceutical agents are incorporated into a delivery system comprising a reverse emulsion, which comprises a disperse polar phase, a continuous lipophilic phase, and one or more emulsifying agents (e.g., a surfactant). The disclosed compositions and methods are useful in the treatment of, for example, gastric <i>H. pylori</i> infection, where the incorporated pharmaceutical agent is an antibiotic.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

Methods For Delivering Pharmaceutical Agents To Mucosal Surfaces

5

FIELD OF THE INVENTION

The present invention relates generally to methods for delivering pharmaceutical agents to mucosal surfaces. More particularly, the present invention relates to methods for delivering therapeutic and diagnostic agents to mucosal surfaces, such as those found in the gastrointestinal (GI) tract and body cavities, using hydrophobic and/or lipophilic delivery systems.

10

BACKGROUND OF THE INVENTION

Over the years, the delivery of drugs and other pharmaceutical agents from an aqueous or hydrophilic environment into or through localized areas of high hydrophobicity has presented one of the greatest challenges in the field of drug delivery. In particular, the hydrophobic nature of the various mucosal surfaces in the body often makes pharmaceutical delivery to those surfaces difficult, especially where the agent to be delivered is hydrophilic. Many delivery systems have been developed for the delivery of pharmaceutical agents to hydrophobic surfaces, including liposomes. However, such delivery systems are often difficult to manufacture or are unstable in certain bodily environments, such as those environments having extreme pH or ionic concentration (e.g., the stomach). Thus, there exists a need for a delivery system that may be used for delivering pharmaceutical agents to mucosal surfaces, especially those of the GI tract.

The efficacy of many pharmaceutical agents is predicated on their ability to proceed to the selected target sites and remain present in effective concentrations for sufficient periods of time to accomplish the desired therapeutic or diagnostic purpose. Difficulty in achieving efficacy may be exacerbated by the location and environment of the target site, as well as by the inherent physical characteristics of the compound administered. For example, drug delivery via routes that are subject to repeated drainage or flushing as part of the body's natural physiological functions offers significant impediments to the effective administration and controlled release of pharmaceutical agents. In this respect, delivery and retention problems are often encountered when administering compounds through the respiratory or gastrointestinal tracts. Repeated administration of fairly large doses is often required to compensate for the

amount of drug washed away and to maintain an effective dosing regimen when employing such routes. Moreover, the molecular properties of the pharmaceutical compound may impair the absorption through a given delivery route, thereby resulting in a substantial reduction in efficacy. This is particularly true of lipophilic compounds that are not soluble in aqueous environments. For instance, insoluble particulates are known to be subject to phagocytosis and pinocytosis, resulting in the accelerated removal of the compound from the target site. Such reductions in delivery and retention time complicate dosing regimes, waste pharmaceutical resources, and generally reduce the overall efficacy of the administered drug.

Unlike many hydrophilic compounds, the delivery of lipid-soluble or lipophilic drugs by conventional means has been and continues to be problematic. Unfortunately, a number of the most promising therapeutic and diagnostic agents currently under development are relatively insoluble in water. Some are bulky polycyclic molecules whose substantial physical size, coupled with the intrinsic lipophilicity of their molecular structure, has severely limited their use in practical pharmaceutical applications. For instance, the oral administration of lipophilic agents using conventional tablets and capsules suffers the disadvantage of a variable rate of absorption and depends on factors such as the presence or absence of food, the pH of gastrointestinal fluids, and gastric emptying rates. Moreover, the degradation of labile drugs by gastric fluids and drug metabolizing enzymes may reduce the drug bioavailability to the point of therapeutic failure.

Methods and formulations have been developed in the art to achieve the efficient local delivery of therapeutic or diagnostic agents to particular regions of the body. For example, aqueous liquids which can be applied at room temperature in a free-flowing state, but which form a semi-solid gel when warmed to body temperature, have been used. Such systems combine ease of application with greater retention at the site of application than the use of exclusively free-flowing vehicles. For example, in U.S. Pat. No. 4,188,373, the disclosure of which is incorporated herein by reference, Pluronic® polyols are used in aqueous compositions to provide thermally gelling aqueous systems. In addition, U.S. Pat. Nos. 4,474,751, 4,474,752, 4,474,753, and 4,478,822, the disclosures of which are incorporated herein by reference, disclose drug delivery systems which utilize thermosetting gels. In these systems, both the gel transition temperature and the rigidity of the gel may be modified by adjusting the pH and/or the ionic strength of the formulation, as well as by adjusting the concentration of the polymer. However, none of these prior efforts completely resolved the

issue of effectively delivering therapeutic agents to a hydrophobic environment, such as a mucosal surface.

Accordingly, it is one object of the present invention to provide gel compositions and methods of their use which effect the delivery of pharmaceutical agents to (or through) hydrophobic environments. Another object of the present invention is to provide gel compositions and methods for the effective treatment of gastric *Helicobacter pylori* (*H. pylori*) infection and peptic ulcers by targeting antibiotic delivery directly to the site of *H. pylori* infection in the hydrophobic mucus lining of the stomach.

10

SUMMARY OF THE INVENTION

The present invention provides a delivery system and a method for delivering pharmaceutical agents (e.g., therapeutic or diagnostic agents) to mucosal surfaces. As a result, the present invention is useful for the topical treatment of diseases of the mucosal surfaces of the gastrointestinal tract and of other body cavities. For example, the present invention may be used to treat various infections, lesions, and cancers by incorporating the appropriate pharmaceutical agent into the hydrophobic delivery system. Infections which may be treated by incorporating antimicrobial or antibiotic agents into the delivery systems of the present invention include, but are not limited to, the following: (1) bacterial infections, such as infection of the stomach by *Helicobacter pylori* (*H. pylori*); (2) protozoan infections, such as infections of the intestines by Giardiasis, Cryptosporidium, Isospora, and Cyclospora; (3) fungal and viral infections; and (4) multibacterial infections, such as found in oral periodontal disease. Cancers and pre-cancerous lesions may also be treated by incorporating neoplastic or chemotherapeutic agents into the delivery systems of the present invention. In this manner, the delivery systems and methods of delivery of the present invention may be used to treat esophageal diseases including disorders of the gastro-esophageal junction, superficial gastric cancers, gastritis including atrophic gastritis, intestinal lymphomas, and sites of precancerous polyps, among other conditions. The delivery systems of the present invention may be formulated for oral, rectal, or vaginal administration, as appropriate for the given application.

20

The present invention is particularly useful in the treatment of *H. pylori* infection, the primary cause of peptic ulcer disease, which has been strongly linked to stomach cancer. The current standard regimen for the treatment of gastric *H. pylori* infection includes three or four

antibiotics administered in tandem with a proton pump inhibitor for two weeks. Such a regimen, however, is expensive, invites non-compliance, and favors emergence of resistant organisms. Furthermore, at best, this regimen eradicates *H. pylori* in only 80%-90% of treated patients. Moreover, in those treated, the rate of emergence of resistant organisms has
5 not yet been determined.

The improved treatment of gastric *H. pylori* infection provided by one embodiment of the present invention results from consideration of the biology of the *H. pylori* organism and its ecology. Most *H. pylori* live in the gastric mucus, with a minority of the organisms attaching to but not invading the lining cells of the stomach. While the most effective
10 treatment of *H. pylori* is by topical administration of antibiotics, treatment with antibiotics is often unsuccessful. This lack of success is attributable to the fact that antibiotics gain access to gastric *H. pylori* only after going through the stomach, being absorbed in the small intestine, and returning to the gastric mucus by systemic circulation. Therefore, the antibiotic leaves the stomach after only a brief contact with the stomach mucus. The amount of
15 antibiotic returning to the gastric mucus is usually but a small fraction of that originally ingested. In general, however, the effective localized treatment of body tissues, diseases, wounds, and lesions requires that a pharmaceutical agent be in contact with the site of treatment for a sufficient period of time.

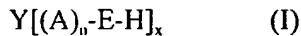
Accordingly, one object of the present invention is to prolong the contact or residence
20 time of pharmaceutical agents, such as antibiotics, with the gastric mucus, thereby facilitating diffusion of the antibiotics into the gastric mucus. The present invention may also be used in the treatment of other infectious or neoplastic diseases that are largely confined to the mucosal surfaces of the GI tract. In this manner, a pharmaceutical agent delivered in a higher concentration locally may be more effective than the lower concentration achieved after
25 gastro-intestinal absorption or parenteral administration.

The present invention provides compositions and methods for delivering a pharmaceutical agent (e.g., a therapeutic or diagnostic agent) to a hydrophobic region of an animal body, such as a mucosal surface. Preferably, the animal is a mammal and, most preferably, is a human. In one preferred embodiment, the delivery system comprises one or
30 more constitutive polymers, such as, for example, polyoxyalkylene block copolymers. Optionally, one or more modifier polymers, such as, for example, carboxymethylcellulose or

a pharmaceutically acceptable salt thereof, and/or one or more hydrophilic co-surfactants may be included in the delivery system.

According to a preferred embodiment, the compositions comprise one or more polyoxyalkylene block polymers of the formula

5



wherein A is a polyoxyalkylene moiety;

x is at least 2;

10 Y is derived from water or an organic compound containing x reactive hydrogen atoms;

E is a polyoxyethylene moiety;

n has a value such that the average molecular weight of A is at least about 500; and

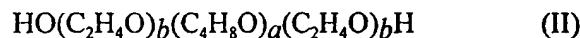
the total average molecular weight of the copolymer is at least about 5000.

Preferably, the polyoxyalkylene moiety A has an oxygen/carbon atom ratio of less
15 than 0.5. According to one embodiment of the invention, A is derived from an alkylene oxide selected from the group consisting of butylene oxide, propylene oxide, or a mixture thereof. Preferably, A is a polyoxypropylene moiety and has an average molecular weight of at least about 1200.

The polyoxyethylene moiety E preferably constitutes at least about 60% by weight of
20 the copolymer. More preferably, E constitutes at least about 70% and, most preferably, at least about 80% by weight of the copolymer.

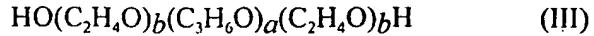
In one embodiment, Y is derived from a water-soluble organic compound having 1 to about 6 carbon atoms. In another embodiment, Y is derived from an organic compound selected from the group consisting of propylene glycol, glycerin, pentaerythritol
25 trimethylolpropane, ethylenediamine and mixtures thereof.

According to one embodiment, the copolymer has the formula (II):



30 wherein a and b are integers such that $(C_4H_8O)_a$ has a molecular weight of at least about 500.

In a more preferred embodiment, the copolymer has the formula:



wherein a and b are integers such that $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of at least about 900.

In another embodiment, the copolymer has the formula (IV):

5



wherein R is $\text{H}(\text{OC}_2\text{H}_4)_b(\text{OC}_3\text{H}_6)_a-$, and a and b are integers such that $(\text{OC}_3\text{H}_6)_a$ has a sum average molecular weight of at least about 1500. As used herein, the term "sum average 10 molecular weight" means the sum of the average molecular weights of all four R groups.

Where a modifier polymer is included in the delivery system formulation, it is preferably a carboxymethylcellulose and, most preferably, is sodium carboxymethylcellulose. Where present, the modifier polymer preferably comprises about 0.05%-10% by weight and, more preferably, about 0.5%-5% by weight of the composition. In addition to or in place of 15 the modifier polymer may be a hydrophilic co-surfactant, such as a fatty acid soap.

In another preferred embodiment, one or more pharmaceutical agents are incorporated into a delivery system comprising a reverse emulsion, which comprises a disperse polar phase, a continuous lipophilic phase, and one or more emulsifying agents. Preferably, the disperse phase comprises one or more pharmaceutical agents. Preferred polar liquids for the 20 disperse phase include water, short-chain alcohols, dimethylsulfoxide (DMSO), polyethylene glycols, and mixtures thereof. Preferably, the continuous phase comprises one or more lipophilic organic compounds, including, for example, hydrocarbon oils, fluorochemicals, and perfluorochemical-hydrocarbon oil mixtures. Emulsifying agents include both fluorinated and non-fluorinated surfactants.

Also disclosed herein is the use of one or more constitutive polymers in the manufacture of a mucosal delivery system, wherein the mucosal delivery system is a liquid at room temperature or below and a gel at mammalian body temperature.

In addition, disclosed herein is the use of a reverse emulsion in the manufacture of a mucosal delivery system, wherein the mucosal delivery system comprises a disperse polar 30 phase, a continuous lipophilic phase, and one or more emulsifying agents.

DETAILED DESCRIPTION OF THE INVENTION

Compositions and methods are disclosed herein for the delivery of pharmaceutical agents (e.g., therapeutic or diagnostic agents) to the mucosal surfaces of animals, particularly those of the gastrointestinal tract and of the oral cavity. In certain embodiments, the 5 compositions of the present invention are delivery systems comprising one or more constitutive polymers and, optionally, one or more modifier polymers and/or one or more hydrophilic co-surfactants.

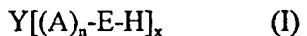
I. Polymer Gel Delivery Systems

10 A. Constitutive Polymers

The present invention provides in certain embodiments delivery systems comprising one or more constitutive polymers dispersed in an aqueous medium. In a preferred embodiment, the constitutive polymer is a polyoxyalkylene polymer. More preferably, the constitutive polymer is selected from the group consisting of polyoxyalkylene block 15 copolymers, polyoxyalkylene polyethers, and combinations thereof. In especially preferred embodiments, the constitutive polymer is Poloxamer 407.

The constitutive polymer or polymers may be present at any concentration that results in the desired gel viscosity and/or viscoelastic properties. Preferably, the constitutive polymers are present in a concentration which, when combined with the other components of 20 the delivery system, permits administration as a relatively free-flowing liquid that gels upon contact with mammalian tissue. In this manner, the present invention takes advantage of the gelation properties of the one or more constitutive polymers. Specifically, at certain concentrations, aqueous solutions of said polymers form gels at mammalian body temperatures but are liquids at ambient temperatures or below.

25 According to a preferred embodiment, the delivery systems of the present invention comprise one or more polyoxyalkylene block copolymers of the formula



30 wherein A is a polyoxyalkylene moiety;
x is at least 2;

Y is derived from water or an organic compound containing x reactive hydrogen atoms;

E is a polyoxyethylene moiety;

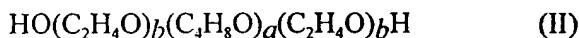
n has a value such that the average molecular weight of A is at least about 500; and the total average molecular weight of the copolymer is at least about 5000.

Preferably, the polyoxyalkylene moiety A has an oxygen/carbon atom ratio of less than 0.5. According to one embodiment of the invention, A is derived from an alkylene oxide selected from the group consisting of butylene oxide, propylene oxide, or a mixture thereof. Preferably, A is a polyoxypropylene moiety, which preferably has an average molecular weight of at least about 1200.

The polyoxyethylene moiety E preferably constitutes at least about 60% by weight of the copolymer. More preferably, E constitutes at least about 70% and, most preferably, at least about 80% by weight of the copolymer.

In one embodiment, Y is derived from a water-soluble organic compound having 1 to about 6 carbon atoms. In another embodiment, Y is derived from an organic compound selected from the group consisting of propylene glycol, glycerin, pentaerythritol trimethylolpropane, ethylenediamine, and mixtures thereof.

According to one preferred embodiment, the copolymer has the formula (II):



wherein a and b are integers such that the hydrophobe base represented by $(\text{C}_4\text{H}_8\text{O})_a$ has a molecular weight of at least about 500, preferably at least about 1000 and, most preferably, at least about 3000, as determined by hydroxyl number. The copolymer is characterized in that all of the hydrophobic oxybutylene groups are present in chains bonded to an organic radical at the former site of a reactive hydrogen atom, thereby constituting a polyoxybutylene base copolymer. The hydrophilic oxyethylene groups are used to cap the polyoxybutylene base polymer.

Useful polyoxyalkylene block copolymers which will form gels in aqueous solutions can be prepared using a hydrophobe base (such as A in Formula (I)) derived from propylene oxide, butylene oxide, or mixtures thereof. These block copolymers and representative methods of preparation are further generally described in U.S. Pat. Nos. 2,677,700, 2,674,619, and 2,979,528, the disclosures of which are incorporated herein by reference.

Generally, the polyoxybutylene-based block copolymers useful in the present invention are prepared by first condensing 1,2-butylene oxide with a water-soluble organic compound initiator containing 1 to about 6 carbon atoms, such as 1,4-butylene glycol or propylene glycol, and at least 2 reactive hydrogen atoms to prepare a polyoxyalkylene polymer hydrophobe of at least about 500, preferably at least about 1000 and, most preferably at least about 1500 average molecular weight. Subsequently, the hydrophobe is capped with an ethylene oxide residue. Specific methods for preparing these compounds are described in U.S. Pat. No. 2,828,345 and British Patent No. 722,746, both of which are incorporated herein by reference.

In a further preferred embodiment, the compositions comprise polyoxyethylene-polyoxypropylene block copolymers of the formula (III):



wherein a is an integer such that the hydrophobe base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of at least about 900, preferably at least about 2500 and, most preferably, at least about 4000 average molecular weight, as determined by the hydroxyl number. In a particularly preferred embodiment, the compositions comprise a polyoxyethylene-polyoxypropylene block copolymer of formula (III), having a polyoxypropylene hydrophobe base average molecular weight of about 4000, a total average molecular weight of about 12,000, and containing oxyethylene groups in the amount of about 70% by weight of the total weight of the copolymer. This copolymer is sold under the trademark PLURONIC® F-127 (also known as Poloxamer 407)(BASF Corp, Parsippany, N.J.).

More specifically, Poloxamer 407 is a tri-block copolymer containing two polyoxyethylene blocks flanking a central polyoxypropylene block. The USP material has an average molecular formula of $(\text{EO})_{101}-(\text{PO})_{56}-(\text{EO})_{101}$ and an average molecular weight of about 12,000. When placed in an aqueous solution in accordance with the present invention, Poloxamer 407 self-assembles into micelles so as to remove contact between the polyoxypropylene groups and water; self-assembly is apparently driven by hydrophobic forces. The structure of the micelles and the interactions between them are strongly dependent on temperature. Interestingly, a large increase in solution viscosity (i.e., gel-phase

formation) is noted with increased temperature. Gel-phase formation occurs as a result of organization of the micelles into a three-dimensional cubic array.

In yet another embodiment, polyoxyethylene-polyoxypropylene block copolymers having the formula (IV) are used:

5



wherein R is $H(OC_2H_4)_b(OC_3H_6)_a-$, and a and b are integers such that the hydrophobe base represented by $(C_3H_6O)_a$ has a sum average molecular weight of at least about 2000,

10 preferably at least about 3000 and, most preferably, at least about 5000. The hydrophobe base is prepared by adding propylene oxide for reaction at the site of the four reactive hydrogen atoms on the amine groups of ethylenediamine. An ethylene oxide residue is used to cap the hydrophobe base.

15 In all permutations of copolymers of formula (I), it is preferred that the polyoxyethylene chain constitutes about 60%, preferably at least about 70% and, most preferably, at least about 80% by weight of the copolymer. It is further preferred that the copolymer have a total average molecular weight of at least about 5000, preferably at least about 10,000 and, most preferably, at least about 15,000.

20 The procedure used to prepare aqueous solutions that form gels of the polyoxyalkylene block copolymers is well known. Either a hot or cold process for forming the solutions can be used. A cold technique involves the steps of dissolving the polyoxyalkylene block copolymer at a temperature of about 3°C to about 10°C in water. When solution is complete, the system is brought to room temperature, whereupon it forms a gel. If the hot process of forming the gel is used, the polymer is added to water heated to a 25 temperature of about 75°C to about 85°C, with slow stirring until a clear homogeneous solution is obtained. Upon cooling, a clear gel is formed. Block copolymer gels containing polyoxybutylene hydrophobes must be prepared by the above hot process, since these will not liquefy at low temperatures.

30 The organic compound initiator that is utilized in the preparation of polyoxyalkylene block copolymers is typically water or an organic compound, and can contain a plurality of reactive hydrogen atoms. Preferably, Y in formula (I) above is derived from a water-soluble organic compound having 1 to about 6 carbon atoms and containing x reactive hydrogen

atoms where x has a value of at least 1 and, preferably, a value of at least 2. Falling within the scope of the compounds from which Y is derived from water-soluble organic compounds having at least two reactive hydrogen atoms are water-soluble organic compounds such as propylene glycol, glycerin, pentaerythritol, trimethylolpropane, ethylenediamine, mixtures thereof, and the like.

The oxypropylene chains can optionally contain small amounts of at least one of oxyethylene or oxybutylene groups. Oxyethylene chains can optionally contain small amounts of at least one of oxypropylene or oxybutylene groups. Oxybutylene chains can optionally contain small amounts of at least one of oxyethylene or oxypropylene groups. The physical form of the polyoxyalkylene block copolymers may be a viscous liquid, a paste, or a solid granular material, depending upon the molecular weight of the polymer.

In addition to those polyoxyalkylene polymers described above, the present compositions may comprise other polyoxyalkylene polymers that form gels at low concentrations in water. Examples of such polymers are described in U.S. Pat. No. 15 4,810,503, the disclosure of which is incorporated herein by reference. These polymers are prepared by capping conventional polyoxyalkylene polyether polyols with an alphaolefin epoxide having an average of about 20 to about 45 carbon atoms, or mixtures thereof. Aqueous solutions of these polymers gel in combination with surfactants, which can be ionic or nonionic. The combination of the capped polyether polymers and the surfactants provide 20 aqueous gels at low concentrations of the capped polymer and surfactant, which generally do not exceed 10% by weight.

Conventional copolymer polyether polyols are prepared by preparing block or heretic intermediate polymers of ethylene oxide and at least one lower alkylene oxide having 3 to 4 carbon atoms as intermediates. These are then capped with the alpha-olefin epoxide. 25 Ethylene oxide homopolymers capped with the alpha-olefin oxides are also useful as intermediates.

The heretic copolymer intermediate is prepared by mixing: (i) ethylene oxide and at least one lower alkylene oxide having 3 to 4 carbon atoms with (ii) a low molecular weight active hydrogen-containing compound initiator having at least two active hydrogens and, 30 preferably, 2 to about 6 active hydrogen atoms; one example of (ii) is a polyhydric alcohol containing from 2 to about 10 carbon atoms and from 2 to about 6 hydroxyl groups. The mixture is then heated to a temperature between about 50°C and about 150°C (preferably,

between about 80°C and about 130°C), under an inert gas pressure, which is preferably about 30-90 psig.

A block copolymer intermediate is prepared by reacting either the ethylene oxide or the alkylene oxide having 3 to 4 carbon atoms with the active hydrogen-containing
5 compound, followed by reaction with the other alkylene oxide.

The ethylene oxide and the alkylene oxides having from 3 to 4 carbon atoms are used in the intermediates in amounts so that the resulting polyether product will contain at least 10% by weight and, preferably, between about 70% and about 90% by weight, of ethylene oxide residue. The ethylene oxide homopolymer intermediate is prepared by reacting
10 ethylene oxide with the active hydrogen-containing compound. The reaction conditions for preparing the block copolymer and ethylene oxide homopolymer intermediates are similar to those for the heretic copolymer intermediate. The temperature and pressure are maintained in the above ranges for a period of about one hour to about ten hours, preferably between about one and about three hours.

15 The alpha-olefin oxides that are utilized to modify the conventional polyether intermediates are those oxides, and commercially available mixtures thereof, containing an average of about 20 to about 45, preferably about 20 to about 30, carbon atoms. The amount of alpha-olefin required to obtain the more efficient capped polyethers is generally about 0.3-10%, preferably about 4-8 percent, of the total weight of the polyethers.

20 Further description regarding the preparation of heretic and block copolymers of alkylene oxides and ethylene oxide homopolymers is provided in U.S. Pat. Nos. 3,829,506, 3,535,307, 3,036,118, 2,979,578, 2,677,700, and 2,675,619, which are incorporated herein by reference.

25 Whatever constitutive polymer is selected, the absolute concentration present in the compositions is determined by the gelation characteristics desired. One major advantage of the present invention is that the desired gelation temperatures and viscosity of the resulting gels may be adjusted through the addition of modifier polymers and hydrophilic co-surfactants. This allows the use of a lower concentration of constitutive polymer, without markedly reducing the ultimate gel characteristics of the composition. Exemplary
30 concentrations of constitutive polymer are about 2%-50% w/w and, more preferably, about 4%-30% w/w and, even more preferably, about 16%-28% w/w.

As used herein, the term "polyalkylene block polymers" include those polymers which form clear gels at mammalian body temperatures but are liquids at ambient temperatures or below.

As used herein, the term "gel" is defined as a solid or semisolid colloid containing a 5 certain quantity of water. A colloidal solution with water is often called a "hydrosol."

B. Modifier Polymers

The delivery systems of the present invention optionally comprise one or more modifier polymers. Any biocompatible modifier polymer that modifies the dissolution time 10 of the gel resulting from the administration of the compositions of the present invention may be used in accordance with the teachings herein. Preferably, the modifier polymer has the following characteristics: (a) high molecular weight; (b) effective swelling, but poor dissolution, in water; (c) compatibility with the constitutive polymer; and (d) stability to extremes in heat and pH. Those skilled in the art will appreciate that the phrase "alter the 15 dissolution time" refers to alteration of the gel dissolution time *in vitro* or *in vivo* with respect to a gel comprising constitutive polymer without the modifier polymer under similar conditions.

Without wishing to be bound to a particular theory, it is presently believed that release (and subsequent gel dissolution) is a function of several physicochemical characteristics 20 within the gel, which can be modified by the addition of high molecular weight modifier polymers, examples of which include carboxymethylcellulose (particularly, sodium carboxymethylcellulose), polyacrylates (i.e. Carbopol), and polyester-based polymers. The dissolution rate is apparently modified by the formation of a strong modifier polymer matrix that controls the release of the constitutive polymer via diffusion through the interstices of the 25 modifier polymer matrix. One possible reason for the altered dissolution rate may be that the constitutive polymer has to diffuse around the long linear molecules of the incorporated modifier polymer. In general, the effect on dissolution rate appears to be most pronounced where the selected modifier polymer has a molecular weight greater than or equal to approximately 500,000, although modifier polymers of much lower molecular weight (i.e., on 30 the order of 50,000) also exhibit this effect. In particularly preferred embodiments, the one or more modifier polymers combine a relatively high molecular weight with a biodegradable moiety in their structure to speed excretion. High molecular weight polylactide-co-glycolide

copolymers, which are broken down by hydrolytic decomposition, are examples of such modifier polymers. It should be emphasized that a modifier polymer may also be used to slow the dissolution (and hence prolong delivery time) of any incorporated pharmaceutical agent.

- 5 While any polymeric entity possessing the appropriate characteristics may be incorporated in the compositions of the present invention, exemplary modifier polymers compatible with the teachings herein include, but are not limited to, the following: poly(acrylic acid), poly(styrene sulfonate), carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose,
- 10 hydroxyethylmethylcellulose, poly(vinyl alcohol), poly(ethylene oxide), poly(vinylpyrrolidone), shellac, cellulose acetate phthalate, cellulose acetate succinate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose acetate, poly(methacrylic acid-co-methylmethacrylate), poly(methyl acrylate), poly(methyl methacrylate), poly(glutamic acid), poly(lactic acid), poly(lactide-co-glycolide), poly(glycolic acid), poly(*e*-caprolactone),
- 15 poly(*b*-hydroxybutyric acid), poly(*b*-hydroxyvaleric acid), polydioxanone, poly(ethylene terephthalate), poly (malic acid), poly(tartronic acid), poly(ortho esters), polyanhydrides, polycyanoacrylate, poly(phosphoesters), polyphosphazenes, poly(lysine), polysaccharides, chitosan, polyelectrolytes, gelatin, gum arabic, poly(amino acids), agar, furcelleran, alginate, carageenan, starch, pectin, celluloses, exudate gums, tragacanth, karaya, ghatti seed gums,
- 20 guar gum, locust bean gum, xanthan, pullulan, scleroglucan, curdlan, dextran, gellan, chitin, chondroitin sulfate, dermatan sulfate, heparin, keratan sulfate, hyaluronic acid, and combinations thereof. One embodiment of the present invention includes cross-linked poly(acrylic acid) as a modifier polymer. It will further be appreciated by those skilled in the art that any pharmaceutically acceptable salt of the foregoing compounds may be used in the disclosed compositions without compromising the effectiveness thereof.
- 25

As will be seen in the Examples below, the modifier polymers of the present invention may be used in surprisingly low concentrations to provide extended dissolution times or release times. In this regard, the selected modifier polymers are preferably incorporated in a range between about 0.05% and about 25% by weight and, more preferably, 30 in a range between about 0.5% and about 5% by weight. Of course the absolute amount of modifier polymer included in the composition will depend on factors such as the constitutive polymer selected, the molecular weight of the modifier polymer, and the physiochemical

properties of the various other components. These determinations are well within the purview of the skilled artisan and may easily be determined without undue experimentation.

C. Hydrophilic Co-Surfactants

The delivery systems of the present invention may also comprise one or more hydrophilic co-surfactants, in addition to or in place of the optional modifier polymer(s). The hydrophilic co-surfactants, like the modifier polymer(s), alter the physiochemical properties of the delivery systems, including the gelation temperature. The lower gelation temperature (LGT) refers to the temperature at which poloxamer micelles (sol phase) self-assemble into a cubic array (i.e. the gel phase). At temperatures above the upper gelation temperature (UGT), the micelles change their shape from spheres to prolates, thereby negating their ability to assemble into a cubic packing. This leads to the reformation of the low viscosity sol phase. Above another critical temperature, termed the cloud point (CP), the micelles separate into their own coacervate phase in excess water. The solution clouds due to mixing of the two insoluble phases.

The lower gelation temperature (LGT) of the constitutive polymer solution in water is largely dependent upon the total constitutive polymer concentration, such that increases in concentration lead to decreases in the LGT. Fractionation of the constitutive polymer (as described, for example, in *Textbook of Polymer Science*, F. Billmeyer, Wiley-Interscience, pp. 45-56 (1971)) and the addition of high viscosity carboxymethylcellulose (CMC) does little to alter the LGT.

The equilibrium phase behavior of solutions comprising a constitutive polymer can be dramatically altered by the addition of a hydrophilic co-surfactant. The changes in phase behavior are typically manifested by significant increases in the lower gelation temperature (LGT) and cloud point (CP) temperature.

While any hydrophilic co-surfactant may be used to modify the equilibrium phase behavior of the disclosed compositions in accordance with the teachings herein, hydrophilic co-surfactants comprising fatty acid soaps are particularly compatible with the present invention. In this regard, long-chain, saturated soaps appear to be particularly efficient at altering the phase behavior to provide the desired composition characteristics. Significantly, the rheological properties of the gelled compositions of the present invention are unaltered by the presence of fatty acid soaps, indicating that so as long as the critical packing volume of

the cubic phase is exceeded, the rheology will remain virtually unchanged. Thus, in accordance with the present invention, the addition of hydrophilic co-surfactants to the disclosed polyphase systems provides an efficient method for modifying the LGT and CP temperature. These changes in phase behavior are particularly advantageous for a drug delivery system as they allow for storage and application at temperatures near room temperature. Moreover, these characteristics reduce the potential for significant syneresis during terminal sterilization.

Accordingly, preferred embodiments of the present invention may comprise effective amounts of one or more hydrophilic co-surfactants. In particularly preferred embodiments, the hydrophilic co-surfactant comprises a fatty acid soap. Those skilled in the art will appreciate that fatty acid soaps are GRAS (generally regarded as safe) materials, and are present naturally in the human body. Their toxicological profile is well understood and, at the concentrations compatible with the present invention, they pose no toxicological risk. While several compounds comprising fatty acids are useful in the present invention, particularly compatible fatty acid soaps include sodium oleate, sodium laurate, sodium caprate, sodium caprylate, and combinations thereof.

In any event, as illustrated by certain of the Examples below, the hydrophilic co-surfactants of the present invention may be incorporated in relatively low concentrations to provide the desired gelation properties. It will be appreciated by those skilled in the art that the selected hydrophilic co-surfactants or surfactants may be incorporated at any concentration that provides for the desired gelation temperatures. Exemplary concentrations of hydrophilic co-surfactants compatible with the instant invention are between about 0.05% and about 25% by weight and, more preferably, between about 0.5% and about 5% by weight.

25

II. Reverse Emulsions

In addition to the polymer-based delivery systems described above, a delivery system for delivering pharmaceutical agents to mucosal surfaces comprising a reverse emulsion or microemulsion is also provided by the present invention. The reverse emulsion or microemulsion delivery systems of the present invention comprise a disperse polar phase, a continuous lipophilic phase (henceforth also referred to as the "oil" or "oil phase"), and one or more emulsifying agents (e.g., a surfactant). Preferably, the disperse polar phase comprises one

or more polar, liquid-soluble pharmaceutical agents (e.g., therapeutic or diagnostic agents). Preferably, the continuous lipophilic phase comprises one or more hydrocarbon oils and/or one or more fluorocompounds (e.g., fluorinated or perfluorinated compounds).

5 Optionally, the oil phase may contain one or more solutes capable of increasing the lipophilicity of the oil phase. As will be appreciated by those skilled in the art, a multiple emulsion (e.g., aqueous phase-fluorocarbon-aqueous phase) may be produced by combining the formed reverse emulsion with a continuous aqueous phase.

An emulsion's microstructure is preferably defined as a surfactant monolayer film at a water-oil interface. As will be appreciated by those skilled in the art, the term "water" is not limited to aqueous solutions when discussing emulsions generally. An important property of a surfactant film is its tendency to curve toward either the water or the oil. This tendency of the surfactant film to curve can be quantitatively described by the spontaneous curvature (H_0), an intrinsic property of the surfactant film which depends on the surfactant geometry (i.e., headgroup area, and hydrocarbon tail chain length and volume), the degree of penetration of the oil into the surfactant's hydrocarbon tails, and the degree of hydration of the hydrophilic head groups, among other factors. The sign and value of H_0 not only dictates whether the resulting emulsion will exhibit a normal (oil-in-water) or reverse (water-in-oil) disperse phase system, but also the degree to which it will remain stable. The spontaneous curvature H_0 is considered positive if the film tends to curve toward the oil phase (o/w emulsion) and negative if the film tends to curve toward the aqueous phase (w/o emulsion). The emulsifiers or surfactants are chosen based on their geometry; surfactants are favored which have a small headgroup area and a large tail volume (i.e., an inverted truncated cone or wedge). Surface-active oils may be added to the surfactant system to decrease the spontaneous curvature of the surfactant monolayer. These include, for example, monoglycerides and alcohols, especially long-chain alcohols, sterols, and diglycerides. Specific mineral salts may also be added to reduce the surfactant monolayer spontaneous curvature through the promotion of tight headgroup packing. These include, for example, calcium, magnesium, and aluminum salts.

A. Disperse Polar Phase

30 In a preferred embodiment, the disperse (or discontinuous) polar phase comprises at least one polar liquid for drug solubilization. While numerous polar liquids are compatible with the teachings of the present invention, particularly preferred embodiments incorporate water,

short-chain alcohols, dimethylsulfoxide (DMSO), polyethylene glycols, or mixtures thereof. In another preferred embodiment, the volume of the disperse phase comprises between about 0.05% and 30% of the total volume of the emulsion. More preferably, the disperse phase constitutes about 1%-10% v/v of the total volume of the emulsion.

5 The disperse phase may also contain additives such as mineral salts, buffers, stabilizers, suspending agents, viscosity enhancing agents, preservatives, excipients, oncotic and osmotic agents, nutritive agents, active principals, pharmaceutically active substances, genetic material, or other ingredients designed to enhance various characteristics of the emulsions including their stability, therapeutic efficacy, and tolerance.

10 Suitable water-soluble preservatives that may be employed are sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorabutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol phenyle'hanol, and the like. The disperse phase may also incorporate selected ions to stabilize the emulsion or the encapsulated drug. For example, if the interfacial layer contains phosphatidylglycerol or phosphatidic acid, emulsion stability may be
15 increased by the addition of calcium or magnesium ions into the aqueous phase. In other instances, certain enzymes (e.g. DNase) may require specific ions for stability.

20 The disperse phase may also contain additives (e.g. longer chain polar alcohols such as butanol) designed to suppress Ostwald ripening (irreversible coarsening) in the reverse emulsions. To further improve the solubility of certain drugs (e.g., Taxol) in the emulsions of the invention, ethanol, polyethylene glycols, water-soluble Pluronics®, or dimethylsulfoxide (DMSO) may be added to the disperse phase.

B. Continuous Lipophilic Phase

In a preferred embodiment, the reverse emulsions of the present invention have a
25 continuous oil phase, comprising one or more lipophilic non-fluorinated or fluorinated organic compound(s). Examples of such lipophilic organic compound(s) include, but are not limited to, fluorochemicals, hydrocarbon oils, and perfluorochemical-hydrocarbon oil mixtures. Highly lipophilic oils that facilitate dispersion of the hydrocarbon surfactants in the continuous phase are preferred.

30 Preferred lipophilic oils for use in the continuous phase of the reverse emulsions include fluorocarbon compounds, either totally or partially fluorinated. Lipophilic fluorocarbons containing a halogen atom (e.g., chlorine, bromine, or iodine) or a hydrocarbon moiety (e.g.,

C_2H_5) are particularly preferred. Fluorocarbon molecules used in these emulsions may have various structures, including saturated or unsaturated, straight or branched chain, or cyclic structures, as described, for example, in Riess, J., *Artificial Organs*, 8(1):44-56, 1984. Structural derivatives of fluorochemicals are also contemplated as being within the scope of the 5 present invention.

The totally or partially fluorinated compounds may contain one or more hetero-atoms and/or atoms of bromine or chlorine. The term "partially fluorinated" indicates that at least 10% of the hydrogen atoms in the hydrocarbon oil, or derivative thereof, have been replaced with fluorine atoms. Preferably, these fluorochemicals comprise from 2 to about 16 carbon atoms 10 and include, but are not limited to, linear, cyclic or polycyclic perfluoroalkanes, bis-(perfluoroalkyl)alkenes, perfluoroethers, perfluoroamines, perfluoroalkyl bromides, and perfluoroalkyl chlorides. Exemplary partially fluorinated fluorochemicals that are compatible with the present invention include CF_3CH_2F (FC 134A), $CHF_2CF_2CH_2F$ (FC 245ca), and CHF_2CHF_2 (FC134), among others. The aforementioned compounds may be used either alone 15 or in combination.

In a preferred embodiment of the invention, the incorporated fluorinated compound comprises perfluoroctyl bromide ($C_8F_{17}Br$; PFOB or perflubron), or perfluoroctylethane ($C_8F_{17}C_2H_5$; PFOE). Other preferred fluorochemicals include perfluorooctane (C_8F_{18}), perfluorodecane ($C_{10}F_{22}$), perfluorodecyl bromide ($C_{10}F_{21}Br$; PFDB), bis-(perfluorobutyl)ethene 20 (F-44E), or perfluorodecalin (FDC). In addition to the aforementioned compounds, exemplary fluorochemicals which are contemplated for use in the present invention include halogenated fluorochemicals ($C_nF_{2n+1}X$, $XC_nF_{2n}X$, where $n = 2-10$ and $X = Br, Cl$ or I) and, in particular, 1-bromo-F-butane ($n-C_4F_9Br$), 1-bromo-F-hexane ($n-C_6F_{13}Br$), 1-bromo-F-heptane ($n-C_7F_{15}Br$), 1,4-dibromo-F-butane, and 1,6-dibromo-F-hexane. Other useful brominated fluorochemicals 25 are disclosed in U.S. Patent No. 3,975,512 (to Long), the disclosure of which is incorporated herein by reference. Specific fluorochemicals having chloride substituents, such as perfluoroctyl chloride ($n-C_8F_{17}Cl$), 1,8-dichloro-F-octane ($n-ClC_8F_{16}Cl$), 1,6-dichloro-F-hexane ($n-ClC_6F_{12}Cl$), and 1,4-dichloro-F-butane ($n-ClC_4F_8Cl$) may also be used.

Fluorocarbons, fluorocarbon-hydrocarbon oil compounds and halogenated 30 fluorochemicals containing other linkage groups, such as esters, thioethers and amines are also suitable for use in forming the compositions of the present invention. For instance, compounds having the general formula $C_nF_{2n+1}OC_mF_{2m+1}$ or $C_nF_{2n+1}CH=CHC_mF_{2m+1}$, (as, for example,

$C_4F_9CH=CHC_4F_9$, (*F*-44*E*), $i-C_3F_9CH=CHC_6F_{13}$, (*F*-i36*E*), and $C_6F_{13}CH=CHC_6F_{13}$, (*F*-66*E*)), where *n* and *m* are the same or different, and *n* and *m* are integers from about 2 to about 12 are suitable for use in the present invention. Useful fluorochemical-hydrocarbon diblock and triblock compounds include those with the general formulas $C_nF_{2n+1}-C_mH_{2m+1}$ and $C_nF_{2n+1}C_mH_{2m+1}$, where *n* = 2-12 and *m* = 2-16; or $C_pH_{2p+1}-C_nF_{2n}-C_mH_{2m+1}$, where *p* = 1-12, *m* = 1-12 and *n* = 2-12. Preferred compounds of this type include: $C_8F_{17}C_2H_5$; $C_6F_{13}C_{10}H_{21}$; $C_8F_{17}C_8H_{17}$; $C_6F_{13}CH=CHC_6H_{13}$; and $C_8F_{17}CH=CHC_{10}H_{21}$. Substituted ethers or polyethers (i.e., $XC_nF_{2n}OC_mF_{2m}X$ and $XCFOC_nF_{2n}OCF_2X$, where *n* and *m* = 1-4, and *X* = Br, Cl or I) and fluorochemical-hydrocarbon ether diblocks or triblocks (i.e., $C_nF_{2n+1}-O-C_mH_{2m+1}$, where *n* = 2-10 and *m* = 2-16; or $C_pH_{2p+1}-O-C_nF_{2n}-O-C_mH_{2m+1}$, where *p* = 2-12, *m* = 1-12 and *n* = 2-12) may also be used, as well as $C_nF_{2n+1}O-C_mF_{2m}OC_pH_{2p+1}$, wherein *n*, *m* and *p* have values of from 1-12.

Polycyclic and cyclic fluorochemicals, such as $C_{10}F_{18}$ (*F*-decalin or perfluorodecalin), and a mixture of perfluoroperhydrophenanthrene and of perfluoro n-butyldecalin, are also within the scope of the invention. Additional useful fluorochemicals include perfluorinated amines, such as *F*-tripropylamine ("FTP*A*") and *F*-tributylamine ("FT*B**A*"). *F*-4-methyloctahydroquinolizine ("F*MQ*"), *F*-N-methyl-decahydroisoquinoline ("F*MIQ*"), *F*-N-methyldecahydroquinoline ("F*HQ*"), *F*-N-cyclohexylpyrrolidine ("F*CHP*"), and *F*-2-butyltetrahydrofuran ("FC-75" or "FC-77") may also be used. Other contemplated fluorochemicals having nonfluorine substituents, such as perfluoroctyl hydride and similar compounds having different numbers of carbon atoms, are also useful. Those skilled in the art will further appreciate that various other modified fluorochemicals are suitable for use in the present invention.

Useful fluorocarbons may also be classified by other parameters. In one preferred embodiment, the fluorocarbon used in the continuous phase will have a critical solution temperature versus hexane (CSTH) of less than 10°C. In a particularly preferred embodiment, the selected fluorocarbon will have a CSTH of less than -20°C. In another preferred embodiment, the fluorocarbon will have a molar refractivity less than about 50 cm³ and, most preferably, less than about 40 cm³. In yet another preferred embodiment, the total chain length of the fluorocarbon (*n*+*m*) is less than nine, most preferably six or less.

The continuous oil phase may also comprise "nonamphiphilic" oils to increase its lipophilicity. There are a number of hydrocarbon oils that are contemplated for use in the present invention. These hydrocarbon oils include medium chain triglycerides, or MCT's (i.e.,

triglycerides with greater than 50% C8 and/or C10 and/or C12 and/or C14 fatty acid ester), diglycerides, and monoglycerides. Other suitable hydrocarbon oils may be selected from mineral oils, as well as modified or unmodified naturally derived oils (e.g., soybean, safflower, rapeseed, cottonseed, castor oil, and corn oil). Suitable oils also include, for example, hexane,
5 Freons (e.g., Freon-113) and squalene.

Useful oils (both hydrocarbon-based and fluorochemical) for employment in the present invention may also be classified by other parameters. In one preferred embodiment, the oils used in the continuous phase will have a hydrophile-lipophile balance (HLB) value of less than 15. In a particularly preferred embodiment, the selected oil will have an HLB value of less than
10 10.

Depending on parameters such as formulation, processing, and temperature, the dispersions of the present invention may comprise an emulsion, a microemulsion, a micellar solution, or any other such colloidal system. For example, the dispersion may comprise a transparent, sometimes bluish microemulsion at room temperature and a whitish
15 macroemulsion below room temperature. Particularly preferred embodiments comprise thermodynamically stable microemulsions. As will be appreciated by those skilled in the art, thermodynamically stable microemulsions are resistant to coarsening, which should increase the shelf-life of any incorporated pharmaceutical agent, and are generally characterized by small (average diameter \leq 100 nm) particles having a relatively narrow particle size distribution.
20 Moreover, the homogenous size distribution promotes reproducible delivery profiles and reliable dosing regimens.

In the emulsions of the present invention, the hydrocarbon oil component preferably comprises from about 5% to about 99% (v/v) of the dispersion and, more preferably, from about 50% to about 95% (v/v).

25 Hydrocarbons compatible with the present invention may comprise any organic hydrogenated compound, including derivatives thereof. Hydrocarbon compounds compatible with the present invention include saturated or unsaturated hydrocarbons (cyclic, aliphatic or aromatic), or hydrocarbon derivatives including substituted and unsubstituted compounds (e.g., alcohols, aldehydes, ketones, amines, ethers, amides, etc.) Further, the selected hydrocarbon or
30 hydrocarbons may contain a charged substituent. As indicated above, hydrocarbon oils are particularly preferred. Exemplary biocompatible hydrocarbon oils that may be used include naturally occurring oils such as canola oil, safflower oil, soybean oil, olive oil, corn oil, castor

- oil, sunflower oil and derivatives thereof. Moreover, naturally occurring compounds such as paraffins, waxes, phospholipids, lipids, glycerides and other fatty acid derivatives may be used to form the desired emulsion. For example, triglycerides and, in particular, medium chain triglycerides may be incorporated in the pharmaceutical formulations of the present invention.
- 5 Furthermore, the selected hydrocarbon may be synthetic or partially synthetic. In addition, mixtures of different hydrocarbons, both bioactive and non-bioactive, may be used.

C. Emulsifying Agent

In preferred embodiments, an emulsifying agent comprising one or more fluorinated and/or non-fluorinated surfactants is included. Surfactants are amphiphilic molecules that contain both a hydrophilic "headgroup" and a lipophilic or fluorophilic "tail". The surfactant forms a monomolecular film at the lipophilic/polar liquid (water) interface. The stability of the emulsion is controlled by the spontaneous curvature of the resulting film.

For stable water-in-fluorocarbon emulsions to form, the film must bend toward the water. For this to occur, the surfactant preferably has a small headgroup volume and a large tail volume. Thus, uncharged (nonionic) surfactant headgroups are preferred. Similarly, increasing the degree of unsaturation in the surfactant tail favors reverse emulsion formation. Accordingly, monounsaturated tails (e.g., oleoyl) are particularly preferred. Lysophospholipids containing a single lipid chain and complexed with a divalent cation may also be used.

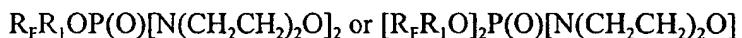
20 In one embodiment of the present invention, the reverse emulsion contains between about 0.01% and 20% w/v of one or more nonfluorinated surfactants. Phospholipids, because of their excellent biocharacteristics, are a particularly preferred class of nonfluorinated surfactants. More particularly, phospholipids that tend to adopt the reverse hexagonal phase at low temperatures and concentrations are favored. Accordingly, phosphatidylethanolamines, 25 phosphatidic acids, and the like are preferred.

Generally, fluorinated surfactants will be preferred when one of the phases comprises a fluorocarbon. In particularly preferred embodiments, the selected fluorinated surfactant will be soluble or dispersible in the fluorocarbon phase and will exhibit a relatively low hydrophile-lipophile balance (HLB). Conversely, for stabilizing emulsions that do not comprise a 30 fluorocarbon, non-fluorinated surfactants typically having a higher HLB will be preferred. Other embodiments may incorporate natural or synthetic polymers and/or polymeric components (surfactants and non-surfactants, soluble or insoluble) to stabilize the emulsions. In

any case, it must be emphasized that both fluorinated and non-fluorinated dispersants, or mixtures thereof, may be used, so long as they provide the desired stabilization.

Fluorinated dispersing agents or dispersants useful in the present invention include fluorinated surfactants which preferably contain at least four fluorine atoms. These fluorinated surfactants can be of different types. Classes of fluorinated surfactants contemplated for use in the present invention include, for example, amphiphiles containing phosphorus (e.g., (perfluoroalkyl)alkylene mono- or dimorpholinophosphate and fluorinated phospholipids) or alcohols, polyols or polyhydroxylated or aminated derivatives including amine oxides and amino acid derivatives. Such fluorinated surfactants are described, for example, in EP-A-0 255 10 443, FR-A- 2 665 705, FR-A- 2 677 360, FR-A- 2 694 559, FR-A- 2 679 150, WO90/15807 US 3,828,085 and EP-A-0311473, and in "Fluorinated Surfactants Intended for Biomedical Uses", J. Greiner, J.G. Riess and P. Vierling in *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, R. Filler, T. Kobayashi and Y. Yagupolski (eds.), Elsevier, 339-380 (1993), each of which is incorporated herein by reference.

In a preferred embodiment, the emulsions of the present invention comprise a (perfluoroalkyl)alkylene phosphate of the formula:



wherein R_F is $CF_3(CF_2)_t$, such that t is from 1 to 11 and R_I is a saturated or unsaturated, linear or branched hydrocarbon chain and both R_F and R_I may contain at least one oxygen and/or sulfur atom.

Other preferred fluorinated surfactants include compounds having at least one fluorinated region and at least one hydrogenated region. For example, hydrogenated/fluorinated compounds of the general formula R_F-W-R_H are particularly useful. In such compounds R_F is a linear, branched, or cyclic highly fluorinated radical having from about 2 to about 14 carbon atoms and optionally including at least one oxygen atom and/or at least one halogenated substituent; R_H is a linear, branched or cyclic saturated or unsaturated hydrocarbon radical having up to about 18 carbon atoms, optionally containing at least one -O- or -S- group; and W is a single bond, oxygen or sulfur.

In a particularly preferred embodiment, R_F is $CF_3(CF_2)_t$, wherein t is from 1 to 11; W is absent and replaced by a single bond, and R_H is a saturated or unsaturated alkyl group of from 1

to 18 atoms. Of course, mixtures of fluorinated surfactants are also contemplated. In either case, the use of such compounds can provide the desired reduction of interfacial tension and associated emulsion stability.

In certain preferred embodiments of the present invention, the fluorinated surfactant 5 comprises diblock molecules, which comprise compounds of the following general formula:



wherein:

10 R_F is one or more perfluorinated or partially fluorinated groups which may or may not contain branches and/or ring structures or hetero-atoms (e.g., $CF_3(CF_2)_m-$ or $CF_3CF_2CF(CF_3)(CF_2)_m-$; m = integer);

R_H is one or more hydrocarbon groups which may or may not contain branches and/or ring structures and/or hetero-atoms and/or multiple bonds (e.g., $-(CH_2)_n-$, $-C_6H_4(CH_2)_4-$, $-(CH_2)_pO(CH_2)_q-$, or $-(CH_2)_2CH=CH(CH_2)_5-$; n, p and q = integer);

15 L is a variable linkage unit and may contain, but is not limited to, one or more of the following: $-CH_2-$, $-CH=CH-$, $-O-$, $-S-$, or $-PO_4-$; and

Z is H or a group more polar or polarizable than the R_H groups (e.g., allyl ethers such as $CF_3(CF_2)_x-(CH_2)_n-O(CH_2)_mCH=CH_2$, or an alcohol, or a halogen, wherein x = 1-11 and n or m = 20 1-16).

More specifically, in particularly preferred embodiments, diblock compounds utilized as dispersants are of the general formula R_FLR_H , where R_F is typically one or more fluorinated alkanes of 2 to about 12 carbon atoms; R_H is one or more linear, branched or cyclic, saturated or unsaturated alkanes of 2 to about 16 carbon atoms; and L is a linkage unit comprising, for 25 example, a single carbon-carbon bond, an oxygen atom, or any other suitable moiety.

In still another preferred embodiment, the diblock compound is selected from the group consisting of compounds having the formula $C_nF_{2n+1}C_mH_{2m+1}$ (saturated), compounds having the formula $C_nF_{2n+1}C_mH_{2m-1}$ (unsaturated), and combinations thereof, wherein n is an integer from 2 to about 12 and m is an integer from 2 to about 16.

30 Besides the aforementioned fluorinated surfactants, non-fluorinated surfactants may also be incorporated in the disclosed emulsions to lower interfacial tension. As with the fluorinated surfactants, these compounds may be present at the interface between the discontinuous phase

and the continuous phase. Such non-fluorinated surfactants, which may comprise a relatively high HLB, are particularly preferred for the stabilization of hydrocarbon oil-water systems whether the hydrocarbon component is present in the discontinuous emulsified phase or in the continuous hydrophobic phase. Again, mixtures of these dispersants are clearly contemplated
5 as being within the scope of the invention.

Exemplary non-fluorinated surfactants compatible with the teachings herein comprise hydrogenated, non-ionic, anionic, cationic or zwitterionic surfactants. Preferred hydrogenated surfactants include, for example, phospholipids, copolymers of the polyoxyethylenepolyoxypropylene type (e.g., PLURONIC F-68[®]) and polyoxyethylene sorbitan esters. More particularly, in preferred embodiments the non-fluorinated surfactant is selected from the group consisting of alcohols, salts of fatty acids, phosphatidylcholines, N-monomethyl-phosphatidylethanolamines, phosphatidic acids, phosphatidyl ethanolamines, N,N-dimethyl-phosphatidyl-ethanolamines, phosphatidyl ethylene glycols, phosphatidylmethanols, phosphatidylethanols, phosphatidylpropanols, phosphatidylbutanols, phosphatidylthioethanols,
10 15 diphytanoyl phosphatides, egg yolk phospholipids, cardiolipins, isomannide monooleates, glycolipids, phosphatidylserines, phosphatidylglycerols and aminoethylphosphonolipids. Preferably, the nonfluorinated surfactant contains at least one mono-unsaturated moiety. In particularly preferred embodiments the nonfluorinated surfactant is 1,2-dioleoylphosphatidic acid or 1,2-dioleoylphosphatidyl ethanolamine.

20 In selected embodiments the non-fluorinated surfactant may exhibit a low hydrophile-lipophile balance. Such surfactants include SPANS[®], BRIJs[®], ethoxylates, dialkyl nonionic surfactants and dialkylzwitterionic surfactants. The emulsion may further comprise a surface active oil capable of decreasing the spontaneous curvature of the surfactant film. Preferably, the surface active oil is a monoglyceride, diglyceride, long-chain alcohol or sterol.

25 Conventional detergents with low hydrophile-lipophile balance (HLB values of about 2-10) may also be used as surfactants. Such detergents include SPANS[®] (sorbitan tetraoleate, sorbitan tetrastearate, sorbitan tristearate, sorbitan tripalmitate, sorbitan trioleate, and sorbitan distearate) and the BRIJ[®] family (e.g., polyoxyethylene 2 stearyl ether). Guerbet alcohol ethoxylates, dialkyl nonionic surfactants, and dialkylzwitterionic surfactants, including betaines
30 and sulfobetaines, are also contemplated for use as emulsifying agents. In addition, other additives that promote steric stabilization of reverse emulsions versus flocculation are anticipated. Preferred additives include block copolymers with low HLB values.

Cosurfactants or surface-active oils that decrease the spontaneous curvature of the resulting emulsion also enhance the stability of the emulsion. Such additives include cholesterol, monoglycerides (e.g., monoolein), diglycerides (e.g., diolein), and alcohols (preferably long-chain alcohols, such as oleoyl alcohol). Because polar liquid-in-fluorocarbon droplets lack any electrostatic repulsive properties, the addition of lipophilic or fluorophilic steric stabilizers (e.g., polymers) is also contemplated. Such additives will help reduce emulsion flocculation and coalescence. Optionally, small amounts of fluorinated or nonfluorinated dialkyl cationic surfactant may be incorporated into the interfacial film to improve cell targeting in gene therapy applications.

In certain embodiments of the present invention, hydrocarbon oil/fluorochemical (HO/FC) dispersions may be used for the controlled delivery of pharmaceutical agents to mucosal surfaces. Both hydrocarbon oil-in-fluorochemical and fluorochemical-in-hydrocarbon oil dispersions are contemplated. In certain embodiments, the dispersed fluorocarbon and/or hydrocarbon oil may comprise a pharmaceutical agent. These dispersions are preferably stabilized through the use of a fluorophilic dispersing agent.

HO/FC preparations have utility as delivery systems and controlled release systems for pharmaceutical agents, and lipophilic materials in general. With the HO/FC dispersions of the present invention, the diffusion of a lipophilic drug, comprising or associated with the encapsulated hydrocarbon oil or fluorocarbon droplet, may be significantly retarded by the dispersed phase interface. These properties allow for controlled drug release and prolonged delivery profiles, particularly for lipophilic pharmaceutical agents. The dispersed phase interface can also act to protect the encapsulated substances from body fluids and vice-versa, thereby reducing the toxicity of the incorporated substances.

To form and stabilize the desired HO/FC preparations, fluorophilic dispersing agents, preferably comprising fluorochemical-hydrocarbon diblocks or fluorinated surfactants, may be incorporated as previously described. The fluorophilic dispersing agent acts at the interface between the incorporated hydrocarbon oil and fluorochemical to allow incorporation of the initially phase-separated hydrocarbon oil in the fluorochemical. As previously discussed, exemplary fluorophilic dispersing agents comprise fluorinated surfactants and fluorochemical-hydrocarbon diblock molecules. Generally, the selected fluorophilic dispersing agent will constitute from about 0.01% to about 99% (v/v) and, more preferably, from about 0.1% to about 50% (v/v) of the HO/FC dispersion.

D. Pharmaceutical Agents

Various hydrophilic, lipophilic, and amphiphilic pharmaceutical agents may be incorporated into the delivery systems of the present invention. Preferably, the 5 pharmaceutical agent is a therapeutic or diagnostic agent. The methods of the present invention are useful for delivering one or more of these pharmaceutical agents to a hydrophobic region of an animal body, such as a mucosal surface.

The emulsions of the present invention are capable of delivering any desired pharmaceutical agent that may be incorporated in either the disperse phase, the continuous 10 phase, or at the interface between the phases. Lipophilic agents may be combined with the dispersion either prior to or after formation. Conversely, any water-soluble pharmaceutical agent may be combined with the continuous phase preparation used to form the selected emulsion. As used herein, the term pharmaceutical agent is defined to mean any pharmaceutical compound or composition, including diagnostic and therapeutic agents, as well as 15 physiologically acceptable gases such as oxygen or nitric oxide, which may be administered to an animal to treat a disorder. Preferred pharmaceutical agents include both hydrophilic drugs with solubility in water, as well as lipophilic drugs. Most preferably, the pharmaceutical agent is a lipophilic agent which is associated with the disperse phase in the case of multiple 20 emulsions, and is primarily associated with the hydrocarbon oil in the case of hydrocarbon oil-in-fluorochemical dispersions.

The present invention may be used to treat infections, lesions, wounds, cancers, diseases, and other conditions affecting any of various mucosal surfaces, including the stomach and intestines (and the remainder of the GI tract), the eyelids, the nostrils and sinuses, the mouth (including the cheeks and gums) and throat (including the esophagus), as 25 well as the vagina, urethra, other regions of the genitals (e.g., in the case of sexually transmitted diseases) and the urinary bladder. Accordingly, the delivery systems may be formulated for oral, rectal, ocular, nasal, vaginal, intraurethral, or intravesical administration, depending on the desired nature and site of treatment. Preferably, the compositions may be administered directly to the site of treatment in order to maximize topical contact.

30 Particularly preferred pharmaceutical agents include, but are not limited to, the following: antibiotics, antimicrobials, antivirals, antifungals, anti-inflammatory agents, analgesics, anesthetics, antihistamines, bactericides, disinfectants, mydriatics,

antiglaucomals, ophthalmic agents, enzymes, cardiovascular agents, polynucleotides, genetic material, viral vectors, immunoactive agents, imaging agents, immunosuppressive agents, peptides, proteins, physiological gases, gastrointestinal agents, chemotherapeutic agents, antineoplastics, antacids, antiulcer agents, respiratory agents, bronchodilators,
5 bronchorestrictors, vasoconstrictors, and combinations thereof. The pharmaceutical agents may be dissolved in or suspended or dispersed in the delivery system formulation.

Other exemplary pharmaceutical agents include α/β adrenergic blockers (e.g., Normodyne and Trandate), angiotensin-converting enzyme inhibitors (e.g., Vasotec), antiarrhythmics, beta blockers, calcium channel blockers, inotropic agents, vasopressors, and
10 ophthalmic agents (e.g., polymyxin B, neomycin, and gramicidin).

The precise amount of pharmaceutical agent incorporated into the delivery systems of the present invention is dependent upon the agent of choice, the required dose, and the form of the agent actually used for incorporation. Those skilled in the art will appreciate that such determinations may be made using well-known pharmacological techniques in combination
15 with the teachings herein.

Examples of anti-inflammatory agents include the glucocorticosteroids (i.e., cortisone, prednisone, prednisolone, dexamethasone, betamethasone, beclomethasone dipropionate, triamcinolone acetonide, and Flunisolide).

Examples of chemotherapeutic and antineoplastic agents useful for incorporation in
20 the delivery systems of the present invention include cyclophosphamide, lomustine, methotrexate, cisplatin, carboxy platin, taxane derivatives, sulfamine, sulfathiazole sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, and nitrofurazone.

Examples of antiviral agents include protease inhibitors, thymidine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment
25 and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, vidarabine, and ganciclovir.

Examples of bronchodilators include the B_2 -agonists (i.e., adrenaline, isoprenaline, salmeterol, salbutamol, terbutaline, formoterol).

Examples of antihistamines include diphenhydramine hydrochloride,
30 diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, and methdilazine hydrochloride.

Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, procaine hydrochloride, tetracaine, tetracaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, and dyclonine hydrochloride.

5 Examples of bactericides and disinfectants include phenol, thymol, benzethonium chloride, chlorhexidine, eugenol, and trimethylammonium bromide.

Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, and tramazoline hydrochloride.

10 A particularly preferred mucosal surface is the mucosal lining of the stomach and the intestines (GI tract) of a mammal. In this application, the preferred pharmaceutical agent is an antibiotic that is effective to treat *H. pylori* infection and peptic ulcers. Particularly preferred antibiotic agents for use in the present invention include, among others, cephalosporins, macolides, quinolones, tetracycline, chlortetracycline, oxytetracycline, 15 penicillin, meticillin, oxacillin, cefalotin, cefalordin, lincomycin, kanamycin, metacycline, chloramphenicol, streptomycin, bacitracin, cycloserine, metronidazole, clarithromycin, gentamicin, amoxicillin, and erythromycin, as well as bismuth salts.

Other particularly preferred mucosal surfaces for targeting in the present invention include the mucosal surfaces within the mouth or oral cavity, such as the tongue, cheeks, 20 gums, palate, throat, and esophagus. Diseases of the oral cavity that may be treated using the present invention include oral mucosal ulcers or lesions caused by viral infections, including herpes simplex, varicella-zoster and herpangina. Antiviral agents such as acyclovir, vidarabine, and ganciclovir, and anesthetics, such as lidocaine, are useful for treating these viral infections. Other diseases of the oral cavity include mycotic infections, such as 25 actinomycosis, histoplasmosis, coccidioidomycosis, and candidiasis. Such mycotic infections may be treated with delivery systems incorporating, for example, penicillin or amoxicillin (for actinomycosis), or amphotericin B, itraconazole, clotrimazole, ketoconazole, or miconazole. Periodontal disease, caused by various bacterial infections, may be treated by any of a variety of antibiotics, including tetracycline, doxycycline, metranidazole, 30 minocycline, amoxicillin, and ciprofloxacin. Infectious diseases of the esophagus that may be treated using the delivery systems of the present invention include candidiasis (*aka* thrush, which is common among infants, the elderly, and the immunocompromised), by the

incorporation of, for example, an azole antifungal or of amphotericin B; herpes simplex and varicella-zoster, by the incorporation of, for example, acyclovir; and cytomegalovirus (CMV), by the incorporation of ganciclovir or foscarnet. Gastroesophageal reflux disease may also be treated, by the incorporation of, for example, H₂ blockers, metoclopramide, or 5 sucralfate. Esophageal cancer may also be treated, by the incorporation of one or more of, for example, cis-platinum, tamoxifen, or 5-fluorouracil.

The following Examples illustrate various aspects of the invention, but are not intended to limit its scope. Where not otherwise specified throughout this specification and claims, temperatures are given in degrees centigrade, and parts, percentages, and proportions 10 are by weight.

EXAMPLE 1

Synthesis of Delivery Systems Comprising Constitutive and Modifier Polymers

Compositions comprising a constitutive polymer (Poloxamer 407) and a modifier 15 polymer (Sodium Carboxymethylcellulose) were prepared by dissolving the Poloxamer 407 in distilled water (4°C) to give a concentration of 28% by weight in accordance with the cold process described above for forming aqueous solutions.

Formulation 1: FloGel 28B (Control)

	<u>Ingredients</u>	<u>Source</u>	<u>Lot</u>	<u>%w/w</u>	<u>grams</u>
20	Poloxamer 407, NF, Prill	BASF	WPDP-586B	28.0000	280.00
	Tromethamine (TRIS), USP	Spectrum	ID 289	0.1091	1.09
	Maleic Acid	Spectrum	IK 051	0.1045	1.05
	Sodium Hydroxide Pellets, USP	Spectrum	IG 043	0.0420	0.42
25	Sterile Water for Irrigation, USP	Baxter	G876094	71.7444	717.44
			Total		1000

Formulation 2 : FloGel 25B/0.5

	<u>Ingredients</u>	<u>Source</u>	<u>Lot</u>	<u>%w/w</u>	<u>grams</u>
30	Poloxamer 407, NF, Prill	BASF	WPDP-586B	25.0000	250.00
	Sodium Carboxymethylcellulose	Spectrum	JA 156	0.5000	5.00
	Tromethamine (TRIS), USP	Spectrum	ID 289	0.1091	1.09
	Maleic Acid	Spectrum	IK 051	0.1045	1.05
	Sodium Hydroxide Pellets, USP	Spectrum	IG 043	0.0420	0.42
35	Sterile Water for Irrigation, USP	Baxter	G876094	74.2444	742.44
			Total		1000

EXAMPLE 2**Retention time of 0.3 ml of 25% poloxamer in mouse stomach.**

Two White Webster mice were administered 0.3 ml of the ice-cold 25% Poloxamer 5 407 in phosphate buffered saline (PBS) through a small gavage tube, after overnight fasting. Each sample contained 0.6g barium sulfate (E-Z-HD). Beginning at 15 minutes, and continuing at 30-minute intervals thereafter, the mice were anesthetized for a few minutes with inhaled Metofane (to minimize alterations of gastrointestinal motility) and the movement of the formulations was followed by serial X-rays beginning 15 minutes after 10 gavage.

The poloxamer formulation was still visible in the stomach by X-rays at six hours, while a control formulation (0.6 g E-Z-HD in cold PBS) was not visible after 1 hour. No side effects were observed in either mouse. When Poloxamer 407 (25%) was given to five mice to determine the variation in gastrointestinal kinetics, all mice had the formulation in the 15 stomach for at least 3 hours, but there was some variation in amount perhaps related to gastrointestinal spasm induced by gavage.

EXAMPLE 3**Retention time of 0.1 ml of 25% poloxamer/0.8% CMC in mouse stomach**

20 The protocol for mouse retention studies was similar to Example 2: 0.1 ml of 25% Poloxamer 407/0.8% CMC, containing 0.4 g of E-Z-HD was administered to two mice by oral gavage. X-rays were taken shortly after administration, and after one, two, three and five hours after brief anesthesia with inhaled Metofane. Although the lower dose of formulation and the lower total amount of barium reduced contrast in the X-ray films, it was concluded 25 that the formulation had a retention time of more than 4 hours.

EXAMPLE 4**Formulation of antibiotics in Poloxamer and HO/FC diblock formulations**

Antibiotics approved by the FDA include clarithromycin, metronidazole, tetracycline, 30 and amoxicillin, among others. Micronized amoxicillin and erythromycin (micronized by Fluid Energy Aljet, PA) formed a uniform and stable suspension in a poloxamer delivery system at concentrations of 20 mg/ml. A similar result was observed for amoxicillin

incorporated into an HO/FC diblock formulation. Erythromycin dissolved in an MCT formulation, as well as at pH 2 in a poloxamer formulation. Tetracycline and gentamicin dissolved in poloxamer formulations at therapeutic levels.

5

EXAMPLE 5

Efficacy of tetracycline formulated in poloxamer in *Helicobacter*-infected mice

Eight *H. felis* infected mice were divided into 3 groups: three mice were treated with tetracycline in 25% Poloxamer 407, three mice were treated with the same concentration of tetracycline in saline; and two mice served as untreated controls. Similarly, nine *H. pylori* 10 infected mice were divided into groups of 4, 3 and 2 mice, respectively. Mice were given two doses per day (0.3 mg of tetracycline in 0.3 ml of saline or poloxamer per mouse, per dose) orally for seven days. All mice were monitored with the urea breath test for 37 days after completion of the treatment.

All *H. felis* infected mice treated with tetracycline in saline showed reduction in the 15 level of infection by urea breath test at one day, but relapsed by day 7. Similar results were observed for *H. pylori* infected mice treated with tetracycline in saline, where two out of the three mice relapsed by day 27. In contrast, infected mice treated with tetracycline in poloxamer showed significantly lower colonization rates in both *H. pylori* and *H. felis* groups 20 at six weeks, compared to mice that were untreated or treated with tetracycline in saline. The results of these experiments suggest that administration of antibiotics incorporated into hydrophobic delivery systems effectively eradicate *H. pylori* infections.

CLAIMS

We claim:

- 5 1. A method for delivering a pharmaceutical agent to a target mucosal surface of an animal, the method comprising:
incorporating a pharmaceutical agent into a mucosal delivery system; and
administering the mucosal delivery system to the animal to deliver the pharmaceutical agent to the target mucosal surface,
10 wherein the mucosal delivery system comprises one or more constitutive polymers, and is a liquid at room temperature or below and a gel at mammalian body temperature.
2. The method of claim 1 wherein the one or more constitutive polymers comprise a polyoxyalkylene block copolymer.
15
3. The method of claim 2 wherein the polyoxyalkylene block copolymer is of the formula
- $$Y[(A)_n-E-H]_x \quad (I)$$
- 20 wherein A is a polyoxyalkylene moiety;
x is at least 2;
Y is derived from water or an organic compound containing x reactive hydrogen atoms;
- 25 E is a polyoxyethylene moiety;
n has a value such that the average molecular weight of A is at least about 500; and
the total average molecular weight of the copolymer is at least about 5000.
4. The method of claim 1 wherein the delivery system further comprises one or more
30 modifier polymers.

5. The method of claim 4 wherein the one or more modifier polymers comprise a carboxymethylcellulose or a pharmaceutically acceptable salt thereof.
6. The method of claim 5 wherein the delivery system comprises poloxamer 407.
5
7. The method of claim 1 wherein the delivery system further comprises one or more hydrophilic co-surfactants.
8. The method of claim 1 wherein the pharmaceutical agent is an antibiotic.
10
9. The method of claim 8 wherein the target mucosal surface is located in a gastrointestinal tract of an animal.
10. The method of claim 9 for the treatment of gastric *H. pylori* infection.
15
11. A method for delivering a pharmaceutical agent to a target mucosal surface of an animal, the method comprising:
incorporating a pharmaceutical agent into a mucosal delivery system; and
administering the mucosal delivery system to the animal to deliver the pharmaceutical
agent to the target mucosal surface,
wherein the mucosal delivery system is a reverse emulsion comprising a disperse polar phase, a continuous lipophilic phase, and one or more emulsifying agents.
- 20
12. The method of claim 11 wherein the disperse polar phase comprises one or more polar liquids selected from the group consisting of water, dimethylsulfoxide, alcohols, and polyglycols.
25
13. The method of claim 11 wherein the pharmaceutical agent is incorporated into the mucosal delivery system by dissolution in the disperse polar phase.
- 30
14. The method of claim 11 wherein the continuous lipophilic phase comprises one or more hydrocarbon oils and/or fluoroochemicals.

15. The method of claim 11 wherein the one or more emulsifying agents comprise a nonfluorinated surfactant.

5 16. The method of claim 1 wherein the target mucosal surface is located within the oral cavity of an animal.

17. The method of claim 15 wherein the nonfluorinated surfactant comprises a detergent having a hydrophile-lipophile balance value between about 2 and about 10.

10

18. The method of claim 11 wherein the pharmaceutical agent is an antibiotic.

19. The method of claim 18 wherein the target mucosal surface is located in a gastrointestinal tract of an animal.

15

20. The method of claim 19 for the treatment of gastric *H. pylori* infection.

21. The use of one or more constitutive polymers in the manufacture of a mucosal delivery system, wherein the mucosal delivery system is a liquid at room temperature or 20 below and a gel at mammalian body temperature.

22. The use of a reverse emulsion in the manufacture of a mucosal delivery system, wherein the mucosal delivery system comprises a disperse polar phase, a continuous lipophilic phase, and one or more emulsifying agents.

25



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/10, 9/08, 9/107		A3	(11) International Publication Number: WO 99/32152 (43) International Publication Date: 1 July 1999 (01.07.99)
<p>(21) International Application Number: PCT/US98/27410</p> <p>(22) International Filing Date: 23 December 1998 (23.12.98)</p> <p>(30) Priority Data: PCT/US97/23865 23 December 1997 (23.12.97) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): MDV TECHNOLOGIES, INC. [US/US]; 3040 Science Park Road, San Diego, CA 92121 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): KHARITONOV, Vladimir [RU/US]; 2536 San Clemente Terrace, San Diego, CA 92122 (US). RANNEY, Helen, M. [US/US]; 6229 La Jolla Mesa Drive, La Jolla, CA 92037 (US). TREVINO, Leo [US/US]; Apartment 5210, 7665 Palmina Drive, San Diego, CA 92122 (US). FLORE, Stephen, G. [US/US]; 3899 Nobel Drive #1308, San Diego, CA 92122 (US). DELLAMARY, Luis, A. [MX/US]; 838 Redberry Court, San Marcos, CA 92069 (US). REEVE, Lorraine, E. [US/US]; 6192 Webster Church Road, Dexter, MI 48130 (US). WEERS, Jeffry, G. [US/US]; 12191 Salix Way, San Diego, CA 92129 (US).</p>		<p>(74) Agents: BURKE, John, E. et al.; Pillsbury Madison & Sutro, LLP, 1100 New York Avenue, N.W., Washington, DC 20005 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 9 December 1999 (09.12.99)</p>	
<p>(54) Title: METHODS FOR DELIVERING PHARMACEUTICAL AGENTS TO MUCOSAL SURFACES</p> <p>(57) Abstract</p> <p>Delivery systems and methods of delivering pharmaceutical agents to a hydrophobic region of an animal, particularly a mucosal surface, such as the mucosal lining of the gastrointestinal (GI) tract, are disclosed. In one embodiment, one or more pharmaceutical agents are incorporated into a delivery system comprising a constitutive polymer, such as a poloxamer, and, optionally, one or more modifier polymers (e.g., carboxymethylcellulose) and/or one or more hydrophilic co-surfactants (e.g., a fatty acid soap). In another embodiment, one or more pharmaceutical agents are incorporated into a delivery system comprising a reverse emulsion, which comprises a disperse polar phase, a continuous lipophilic phase, and one or more emulsifying agents (e.g., a surfactant). The disclosed compositions and methods are useful in the treatment of, for example, gastric <i>H. pylori</i> infection, where the incorporated pharmaceutical agent is an antibiotic.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
RJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LJ	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/27410

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 6	A61K47/10	A61K9/08
A61K9/107		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 369 131-A (POLI STEFANO ET AL) 29 November 1994 (1994-11-29) column 2, line 14 - line 36 column 6 -column 7; examples 4,7,8 ---	1-3,6,8, 21
X	WO 95 24430 A (ALCON LAB INC ;UNIV WASHINGTON (US)) 14 September 1995 (1995-09-14) page 21, line 34 -page 22, line 5 page 4, line 26 -page 5, line 1 page 14, line 19 -page 15, line 2 page 48 -page 52; example 6 ---	1,2,9,21
X	US 5 484 610 A (BAE YOU H) 16 January 1996 (1996-01-16) column 1, line 6 - line 15 column 5, line 13 - line 21 column 12; examples 3,4 ---	1,9,21
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 October 1999

Date of mailing of the international search report

25.10.1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/27410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 694 310 A (WAKAMOTO PHARMA CO LTD) 31 January 1996 (1996-01-31) page 2, line 5 - line 10 page 4, line 8 - line 11 page 7 - page 14; table 1 ---	1,8,9,21
X	WO 94 03157 A (POLI IND CHIMICA SPA ;POLI STEFANO (IT); MAILLAND FEDERICO (IT); M) 17 February 1994 (1994-02-17) page 1, line 1 - line 10 page 5, line 21 - line 28 page 8, line 5 - line 10 page 11; example 4 ---	1-4,6,7, 21
X	EP 0 551 626 A (LEK TOVARNA FARMACEVTSKIH) 21 July 1993 (1993-07-21) page 3, line 3 - line 15 page 6; table 1 page 10; example 3 ---	1-4,6,21
X	EP 0 455 396 A (MEDIVENTURES INC) 6 November 1991 (1991-11-06) page 5, line 33 - line 42 page 7, line 15 - line 36 page 9; example 2 ---	1-3,6,8, 21
X	WO 96 20696 A (EASTMAN KODAK CO ;RUDDY STEPHEN B (US); EICKHOFF W MARK (US); LIVE) 11 July 1996 (1996-07-11) page 9; example 7 ---	1-3,5, 8-10,21
X	US 5 126 141 A (HENRY RAYMOND L) 30 June 1992 (1992-06-30) column 16 - column 17; examples 1,2 ---	1-4,6,21
X	WO 95 09626 A (SYNTEX INC) 13 April 1995 (1995-04-13) page 10, line 30 - line 42 ---	1-9,21
A	WO 90 04971 A (MDR GROUP INC) 17 May 1990 (1990-05-17) page 21; table 1 ---	1-10,21
X	EP 0 274 431 A (MEDAPHORE INC) 13 July 1988 (1988-07-13) page 32; example 81 page 44; example 162 ---	11-19
X	WO 94 14415 A (HEMAGEN PFC) 7 July 1994 (1994-07-07) page 15; example 1 ---	11-14, 16,17,19
X	EP 0 598 116 A (NIPPON SHINYAKU CO LTD) 25 May 1994 (1994-05-25) page 5; example 1 ---	11-17,19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/27410

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2.

Claims Nos.: 1,21

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3.

Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/27410

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,21

In view of the large number of compounds which are theoretically defined by the expression "constitutive polymers" in Claims 1 and 21, the search has been restricted for economic reasons. The search was limited to the general concepts of "constitutive polymers", to the compounds cited in the description on pages 7-12 and claimed in Claim 2,3,6 and to the relevant IPC groups concerned (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7.; see Rule 33(3) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/27410

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,21

A method for delivering a pharmaceutical agent to a target mucosal surface of an animal, characterized by the use of a mucosal delivery system comprising one or more constitutive polymers, and which is a liquid at room temperature or below and a gel at mammalian temperature.

2. Claims: 11-20, 22

A method for delivering a pharmaceutical agent to a target mucosal surface of an animal, characterized by the use of a mucosal delivery system which is a reverse emulsion system comprising a disperse phase, a continuous lipophilic phase and one or more emulsifying agents.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27410

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5369131	A 29-11-1994	IT 1247529 B EP 0510561 A AT 140623 T CA 2066945 A CS 9201239 A DE 69212371 D DE 69212371 T RU 2093146 C		17-12-1994 28-10-1994 15-08-1996 25-10-1992 18-11-1992 29-08-1996 16-01-1997 20-10-1997
WO 9524430	A 14-09-1995	AU 692852 B AU 2093295 A CA 2184814 A CN 1145080 A EP 0748342 A JP 10500148 T		18-06-1998 25-09-1995 14-09-1995 12-03-1997 18-12-1996 06-01-1998
US 5484610	A 16-01-1996	NONE		
EP 0694310	A 31-01-1996	AU 668447 B AU 5433394 A FI 953575 A NO 953189 A US 5624962 A CA 2153234 A CN 1097593 A HU 71676 A IL 107626 A WO 9423750 A JP 2729859 B		02-05-1996 08-11-1994 26-07-1995 14-08-1995 29-04-1997 27-10-1994 25-01-1995 29-01-1996 30-09-1997 27-10-1994 18-03-1998
WO 9403157	A 17-02-1994	IT 1255460 B AT 135566 T CA 2141026 A DE 69301920 D DE 69301920 T DK 652744 T EP 0652744 A ES 2085166 T GR 3019479 T US 5759566 A US 5654000 A		02-11-1995 15-04-1996 17-02-1994 25-04-1996 08-08-1996 08-07-1996 17-05-1995 16-05-1996 31-07-1996 02-06-1998 05-08-1997
EP 0551626	A 21-07-1993	CA 2085690 A JP 5262670 A		20-06-1993 12-10-1993
EP 0455396	A 06-11-1991	CA 2040460 A,C DE 69124416 D DE 69124416 T DK 455396 T JP 2753152 B JP 4225914 A US 5593683 A US 5300295 A US 5306501 A US 5292516 A US 5298260 A		02-11-1991 13-03-1997 04-09-1997 11-08-1997 18-05-1998 14-08-1992 14-01-1997 05-04-1994 26-04-1994 08-03-1994 29-03-1994
WO 9620696	A 11-07-1996	US 5585108 A		17-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27410

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9620696 A		AU 4425496 A CA 2206998 A EP 0801558 A		24-07-1996 11-07-1996 22-10-1997
US 5126141 A	30-06-1992	US 4911926 A AU 616065 B AU 4441689 A CA 2003009 A DE 68916512 D DE 68916512 T DK 571389 A EP 0369764 A JP 2200638 A JP 6047549 B PH 26319 A US 5135751 A US 5681576 A US 5366735 A		27-03-1990 17-10-1991 24-05-1990 16-05-1990 04-08-1994 27-10-1994 17-05-1990 23-05-1990 08-08-1990 22-06-1994 29-04-1992 04-08-1992 28-10-1997 22-11-1994
WO 9509626 A	13-04-1995	AU 678303 B AU 7920594 A BR 9407728 A CA 2172506 A CN 1132479 A CZ 9600954 A EP 0721335 A FI 961466 A HU 73675 A IL 111116 A JP 9509648 T LT 96039 A, B LV 11428 A LV 11428 B NO 961325 A NZ 274678 A PL 313772 A SG 55007 A SI 9420057 A US 5688529 A ZA 9407683 A		22-05-1997 01-05-1995 12-02-1997 13-04-1995 02-10-1996 12-06-1996 17-07-1996 01-04-1996 30-09-1996 05-04-1998 30-09-1997 25-10-1996 20-08-1996 20-12-1996 01-04-1996 29-07-1999 22-07-1996 21-12-1998 31-10-1996 18-11-1997 01-04-1996
WO 9004971 A	17-05-1990	US 4983585 A		08-01-1991
EP 0274431 A	13-07-1988	US 4794000 A US 4914084 A US 4963367 A AT 105183 T CA 1321542 A DE 3889346 D JP 63239213 A		27-12-1988 03-04-1990 16-10-1990 15-05-1994 24-08-1993 09-06-1994 05-10-1990
WO 9414415 A	07-07-1994	AU 5539294 A CA 2151491 A CN 1093283 A JP 8504811 T NO 952521 A		19-07-1994 07-07-1994 12-10-1994 28-05-1996 22-06-1995
EP 0598116 A	25-05-1994	DE 69027941 D		29-08-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27410

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0598116 A		DE 69027941 T AT 140622 T CA 2069635 A,C ES 2090147 T WO 9107973 A JP 2653245 B	23-01-1997 15-08-1996 28-05-1991 16-10-1996 13-06-1991 17-09-1997